REMARKS

This is in response to the Office Action mailed July 18, 2008. Applicants thank the Examiner for the telephonic interview on October 16, 2008, during which various outstanding issues were discussed. During the interview, the rejections were discussed but no agreement was reached. Applicants believe the present amendments to the claims and the following remarks overcome the rejections and place the application in condition for allowance.

After entry of this amendment, claims 1, 5, 8-11, 13, 15, 18, 19, 29, 32, 47 and 49 are pending. Applicants respectfully request entry of the above claim amendments as they are believed to narrow the remaining issues, to put the claims in condition for allowance or, alternatively, in better form for consideration on appeal. Thus, entry under 37 CFR 1.116 is requested.[1] Claims 18 and 29 have been amended as suggested by the Examiner and find support *inter alia* in the original claims. No new matter has been added.

Double Patenting

Claims 1, 5, 8-11, 13, 15, 18, 19, 29, 32, 47, and 49 stand rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 2, 10-12, 15, 16, 19, and 22-27 of co-pending Application No. 11/251,208. As stated in the Amendment and Reply After Final Office Action With RCE dated May 13, 2008 and Amendment and Reply Under 37 CFR § 1.111 dated May 7, 2007, Applicants will file a terminal disclaimer upon an indication that the claims are allowable.

Claim Rejection – 35 USC § 103

Claims 1, 5, 8-11, 13, 15, 18, 19, 29, 32, 47, and 49 stand rejected under 35 U.S.C. § 103(a) as being obvious over Gan in view of Valvekens and Grant. Applicants respectfully traverse and request reconsideration and withdrawal of the rejection in view of the following remarks.

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[1] While maintaining the rejection under 35 U.S.C. § 103(a), the Examiner cites two new references, Romero *et al.* (hereinafter "Romero") and Samuelsen *et al.* (hereinafter "Samuelsen"), in further support of the obviousness rejection. This presents *de facto* a new rejection. See MPEP § 706.07(a). Since the finality of the rejection is questionable, Applicants should be permitted to make the claim clarification presented in this amendment.

The Examiner states that both Gan and Grant teach that glutaredoxin proteins are implicated in protecting a cell against environmental stresses, and thus, one skilled in the art would have been motivated to express the nucleic acid encoding glutaredoxin protein as taught in Gan in any host cell, including plant cell, to produce a stress-tolerant transgenic plant cell. Office Action at page 5. The Examiner further asserts that it was well known in the art at the time the invention was made that yeast genes can be successfully expressed in plants to obtain expected phenotype. The Examiner cites Romero and Samuelsen to support this assertion. Office Action at page 5. The Examiner concludes that it would have been obvious to one skilled in the art to try to overexpress Gan's glutaredoxin coding sequence in a plant for the purpose of obtaining environmental stress tolerant transgenic plant with a reasonable expectation of success. Office Action at page 6. The Examiner additionally argues that it would have been obvious for one skilled artisan to use Gan's nucleic acid as a DNA marker to identify stress-tolerant transgenic plant with a reasonable expectation of success. Applicants respectfully disagree with the Examiner's characterization of the references and conclusion of obviousness for the reasons of record and for the following additional reasons.

Gan discloses cloning and sequencing of a gene encoding a yeast thioltransferase, the TTR gene. It describes that thioltransferase, also named glutaredoxin, is a small protein involved in many cellular thiol-disulfide oxidoreduction processes. It further describes, as the Examiner noted, that glutaredoxin directly participates in the reduction of low molecular weight and protein disulfides in the presence of glutathione. Additionally, Gan discloses that glutaredoxin regulates other enzyme activities, presumably by changing the redoc status of these enzymes. Although suggesting that glutaredoxin might be more potent than thioredoxin in the transfer of reduction equivalents, Gan does not teach or suggest that glutaredoxin proteins are "implicated in protecting a cell against environmental stresses" as asserted by the Examiner. Nor does Gan teach or suggest overexpressing glutaredoxin would enhance stress resistance in yeast.

Grant discloses differential regulation of glutaredoxin gene expression **in response to** stress conditions in yeast. It describes that the expression of two yeast glutaredoxin genes (GRX1 and GRX2) is **induced** in response to various stress conditions and are activated or negatively regulated in different pathways *via* stress-responsive STRE elements in the promoter region. Based on the differential expression patterns, Grant concludes that the two glutaredoxin

genes play distinct roles in response to stress conditions in yeast. See Grant, Abstract at page 33. Thus, Grant teaches, at the most, that GRX1 and GRX2 are themselves **stress regulated** in yeast. This is not the same as disclosing that overexpressing GRX1 and/or GRX2 would **lead to** an enhanced stress resistance. A cause and an effect are not necessarily interchangeable.

Because Gan teaches only the cloning and sequencing of the TTR gene encoding a yeast glutaredoxin and Grant teaches only that yeast glutaredoxins are stress regulated, neither Gan nor Grant, alone or in combination, provide motivation to enhance stress resistance by overexpressing glutaredoxin in yeast, let alone in plants. Thus, because Gan and Grant, alone or in combination, do not disclose or teach all of the claim limitations, a *prima facie* case of obviousness has not been established[2].

Grant teaches that the expression of GRX1 and GRX2 is altered or modulated under stress conditions in yeast. Grant also discloses, however, that yeast cells respond to changes in environmental conditions by altering the expression of particular **sets of genes**. See Grant at page 34, left Col., 1st full paragraph, and at page 40, right Col., 2nd full paragraph. Thus, Grant provides no basis to expect that expression of either GRX1 or GRX2 alone would provide any stress benefit, either in yeast or in a plant. For this reason, the necessary motivation to combine the references is lacking and the rejection should be reconsidered.

The motivation to combine the references as proposed would require the skilled artisan to have been able to predict that the expression of ORSRP in a plant would confer increased stress resistance. As explained above, Grant does not provide such an expectation. Moreover, for the reason of record (Amendment and Reply After Final Office Action With RCE dated May 13, 2008), the difference in genome size between plants and yeasts renders the effects of expressing a yeast gene in plants unpredictable, let along that the yeast gene to be transformed has no clear functional information as discussed above. Furthermore, due to the fundamental difference

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[2] The Examiner bears the initial burden of establishing *prima facie* obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See *In re Lowry*, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994); see also *Ex parte Alexander*, 86 USPQ2d 1120, 1122 (BPAI 2007) (where the Board reversed the obviousness rejection in part because the Examiner had not identified all the elements of the claim).

between unicellular and multicellular eukaryotes and the subcellular compartmentation, the localization of a protein in yeast does not necessarily correspond to the localization of the same protein when expressed in a plant. Different cellular localization of a protein may subsequently affect the protein function. Thus, it is further unforeseeable as to the potential effect of expressing a yeast gene in plants. For at least the above reasons, one skilled in the art would not have had a reasonable expectation of success from the combined teaching of the cited references of enhanced stress tolerance in a plant by overexpressing a yeast glutaredoxin.

Note also Grant's different experimental objectives. The disclosure is focused upon the role of GRX1/GRX2 in yeast. For this further reason, the skilled artisan would not have combined Grant with the other cited references.

The Examiner cites to Romero and Samuelsen to find that it was well known in the art at the time of the invention that yeast genes can be overexpressed in a plant **to produce an expected phenotype**. Those references do not support the rejection in this case, however, since the phenotype achieved in the cells/plants of the present claims was not expected.

A review of Romero and Samuelsen simply reflects that, when overexpressing a yeast gene in a plant, a predicted phenotype may be achieved based on overexpression of a yeast gene having known function. For instance, in Romero, a yeast trehalose-6-phosphate synthase gene (TPS1) was transformed into tobacco and the production and accumulation of trehalose was observed in transgenic plants. TPS1 was known to be the key enzyme for biosynthesis of trehalose in yeast (see Abstract of Bell et al., Eur. J. Biochem., 1992, 209(3): 951-959, cited in Romero, a copy of the Abstract is attached). Thus, increasing the production and accumulation of trehalose was a predictable phenotype. Similarly, in Samuelsen, yeast Fe(III) reductase genes (FRE1 and FRE2) were transformed into tobacco. Fe(III) reductases were known to be important in Fe acquisition, and it is suggested that manipulation or addition of genes encoding such enzyme in plants may present an avenue for enhancing Fe uptake (Samuelsen, page 51, left Col.). Thus, a phenotype of enhancing Fe(III) reduction was expected in the transgenic tobacco plants upon overexpression of yeast Fe(III) reductase genes.

Neither Romero nor Samuelsen support obviousness in this case, since there was no reasonable expectation from the cited references that overexpression of yeast ORSRP genes in plants would confer a stress-resistant phenotype, for reasons discussed above.

Further supporting the lack of a reasonable expectation of success, the cited references suggest that the function of glutaredoxins was not well known, other than their potential role in protection against reactive oxygen species (ROS). The Grant paper acknowledges that the roles or substrates of yeast glutaredoxins GRX1/GRX2 were yet unknown (see Grant at page 34, left Col.).

Since the cited references provide neither motivation nor an expectation of success, the present invention is only obvious with hindsight. The prior art does not provide a basis to expect that that introduction of ORSRP genes in plants would confer a stress-resistant phenotype. Without an expectation of an improved phenotype, the invention would not have been obvious or even "obvious to try."[3]

For at least these reasons, the obviousness rejection is not supported by "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."[4]

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

This response is filed within the three-month period for response from the mailing of the Office Communication, to and including October 20, 2008, pursuant to 37 CFR § 1.7(a). No fee is believed due. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 13311-00012-US from which the undersigned is authorized to draw.

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[3] It is held that, even post-*KSR*, complete absence of proof of motivation to combine will not suffice in finding obvious. See, e.g.., *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373-74 n.3 (Fed. Cir. 2008).

[4] *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, (Fed. Cir. 2006).

Respectfully submitted,

By /s/ Hui-Ju Wu
Hui-Ju Wu, Ph.D.
Registration No.: 57,209
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
(302) 658-5614 (Fax)
Agent for Applicants

#625370

Attachment: Abstract of Bell et al., Eur. J. Biochem., 1992, 209(3): 951-959.

1: Eur J Biochem. 1992 Nov 1;209(3):951-9.

Characterization of the 56-kDa subunit of yeast trehalose-6-phosphate synthase and cloning of its gene reveal its identity with the product of CIF1, a regulator of carbon catabolite inactivation.

Bell W, Klaassen P, Ohnacker M, Boller T, Herweijer M, Schoppink P, Van der Zee P, Wiemken A.

Botanisches Institut, Universität Basel, Switzerland.

Trehalose-6-phosphate synthase is the key enzyme for biosynthesis of trehalose, the major soluble carbohydrate in resting cells of yeast. This enzyme was purified from a strain of Saccharomyces cerevisiae lacking vacuolar proteases. It was found to be a multimeric protein of 630 kDa. Monoclonal antibodies were raised against its smallest subunit (56 kDa) and used for screening a yeast cDNA library. This yielded an immunopositive cDNA clone of 1.7 kb, containing an open reading frame of 1485 base pairs. Its sequence, called TPS1 (for trehalose-6-phosphate synthase), was represented by a single gene in the yeast genome and was found to be almost identical with the recently sequenced CIF1, a gene important for carbon catabolite inactivation, believed to be allelic with FDP1. A mutant obtained by disruption of TPS1 had a very low activity of trehalose-6-phosphate synthase, indicating that TPS1 is an important component of the enzyme. The mutant also showed a growth defect when transferred from glycerol to glucose, a phenotype similar to that of the cif1 and fdp1 mutants deficient in carbon catabolite inactivation. Thus, the smallest subunit of the biosynthetic enzyme trehalose-6-phosphate synthase appears to have, in addition, a central regulatory role in the carbohydrate metabolism of yeast.

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